31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Neuromagnetic Source Imaging of Abnormal Spontaneous Activity in Tinnitus Patient Modulated by Electrical Cortical Stimulation

Rey René Ramírez, Brian Harris Kopell, Christopher R. Butson,
Wolfgang Gaggl, David R. Friedland, and Sylvain Baillet

Abstract—**Electrical cortical stimulation (CS) of the auditory cortices has been shown to reduce the severity of debilitating tinnitus in some patients. In this study, we performed MEG source imaging of spontaneous brain activity during concurrent CS of the left secondary auditory cortex of a volunteer suffering from right unilateral tinnitus. CS produced MEG artifacts which were successfully sorted and removed using a combination of sensor and source level signal separation and classification techniques. This contribution provides the first proof of concept reporting on analysis of MEG data with concurrent CS. Effects of CS on ongoing brain activity were revealed at the MEG sensor and source levels and indicate CS significantly reduced ongoing brain activity in the lower frequency range (<40Hz), and emphasized its higher (>40Hz), gamma range components. Further, our results show that CS increased the spectral correlation across multiple frequency bands in the low and high gamma ranges, and between the alpha and beta bands of the MEG. Finally, MEG sources localized in the auditory cortices and nearby regions exhibited abnormal spectral activity that was suppressed by CS. These results provide promising evidence in favor of the Thalamocortical Dysrhytmia (TCD) hypothesis of tinnitus, and suggest that CS may prove to be an effective treatment of tinnitus when targeted to brain regions exhibiting abnormal spontaneous activity.**

I. Introduction

TINNITUS is the perception of an auditory stimulus in the absence of external environmental sounds. Subjective tinnitus is a subtype generated in the sensorineural auditory system and cannot be heard by an examiner. About 15% of adults have prolonged tinnitus requiring medical evaluation [1].

Subjective tinnitus has been hypothesized to originate in many areas of the central nervous system, including the cochlea, eighth cranial nerve, brain stem, or cortex, but in practice, there are presently no means to reliably discriminate between these possible origins in a patient. Though the pathophysiology of tinnitus remains poorly understood, there is indirect evidence to suggest that the majority of subjective tinnitus cases are associated with partial deafferentation of the auditory system. This typically occurs via cochlea hair cell loss due to aging, noise, or ototoxic medications. A secondary effect of peripheral deafferentation is central auditory compensation. It is hypothesized that plastic changes within central auditory nuclei try to compensate for reduced peripheral input but secondarily lead to spontaneous neural activity and the percept of sound (i.e., tinnitus).

Although there have been many approaches to treating tinnitus, none have been effective in meaningfully alleviating symptoms. A variety of drugs have been tried on tinnitus patients with poor results. Masking devices and behavioral training techniques (e.g., biofeedback and cognitive therapy) also have had limited success. Electrical stimulation of the cortex has been used recently to treat tinnitus symptoms. DeRidder et al. have extended their seminal findings using this technique to a 12-patient study with over 50% of the patients benefiting from the therapy [2], [3]. Cortical stimulation (CS) was found to be more effective at reducing pure-tone, as opposed to white-noise, tinnitus symptoms in patients with predominantly unilateral tinnitus. In another study, Fenoy et al. reported on a patient with bilateral tinnitus who experienced acute suppression of his tinnitus during subdural electrical stimulation of the right auditory cortex [4]. Our group investigated the feasibility of cortical stimulation in 8 subjects and found no immediate responses. Rather, we identified the likelihood that chronic electrical stimulation could induce cortical changes that ameliorate the tinnitus percept in some individuals [5]. It is the findings from this study that prompt the current study to refine the identification of central targets using multimodal neuroimaging for tinnitus treatment.

A quantitative EEG study by Ashton et al. found discrete localized unilateral foci of high-frequency oscillatory brain activity in the gamma range (>40-80Hz) over the auditory cortex specifically in 8 out of 8 patients experiencing unilateral tinnitus during EEG recording [6]. Interestingly, these "hot spots" were identified in either the left or right auditory cortices irrespectively of the laterality of the tinnitus percept.

An MEG case study by Llinas et al. using magnetic source imaging techniques showed that the patient's unilateral tinnitus percept was accompanied by spontaneous abnormal low and high frequency electromagnetic activity that localized to the contralateral auditory cortex [7]. This abnormal activity was suppressed by auditory stimulation that masked the subjective tinnitus percept and produced

Manuscript received April 23, 2009
All authors are with the Medical College of Wisconsin, Milwaukee, WI 80305, USA.
S. Baillet, C.R. Butson and R.R. Ramirez are with the Dept of Neurology (phone: 414-805-1104; fax: 414-805-1103; e-mail: sbaillet@mcw.edu, cbutson@mcw.edu, rrramirez@mcw.edu).
B.H. Kopell is with the Dept of Neurosurgery (e-mail: bkopell@mcw.edu).
W. Gaggl is with the Dept of Radiology (e-mail: wgaggl@mcw.edu).
D.R. Friedland is with the Dept of Otolaryngology (e-mail: DFriedland@mcw.edu).

residual inhibition. Consistent with these results, Weisz et al. found that the spontaneous electromagnetic brain activity in tinnitus patients was reduced in the alpha range (8-12Hz) and increased in the delta range (1.5-4Hz) in temporal brain areas [8] and that the residual inhibition of tinnitus intensity produced by masking stimuli was correlated with a reduction of delta power, also in temporal regions [9]. Moreover, a neurofeedback study showed that reducing delta (0.5-4Hz) power and enhancing tau (8-12Hz) power using EEG-based neurofeedback abolished the tinnitus sensation in patients that were able to modify their brain oscillations [10]. Other MEG studies have also suggested that tinnitus patients have abnormal functional source connectivity during resting and auditory processing [11].

These studies reporting on global electrophysiological measures of tinnitus-related brain activity may be interpreted along the lines of the general assumption of thalamo-cortical dysrhythmia (TCD) [7], [12], [13]. TCD predicts that low-frequency thalamocortical bursting produces a center of low-frequency oscillatory activity in the auditory cortex (as if this local thalamocortical circuit had fallen asleep), which in turn laterally disinhibits the surrounding auditory cortical areas thereby causing them to fire spontaneously in the higher frequency range (gamma/beta) of MEG/EEG signals. According to the TCD hypothesis, the positive symptoms of tinnitus are produced by such spontaneous abnormal high-frequency activity in areas of the auditory cortices mapped to the tinnitus percept spectral contents. It is further claimed that the tinnitus percept may be suppressed by reducing either the center-organized abnormal low-frequency oscillations that produce the disinhibition, or the surround-organized high frequency oscillations.

This multimodal body of evidence suggests that bilateral and unilateral tinnitus is amenable to targeted stimulation applied at a single cortical site. Although both unilateral and bilateral tinnitus are often cortically-lateralized, it is not straightforward to predict on what side of the cortex the tinnitus activity is likely to manifest based solely on the laterality of the tinnitus perception. Therefore, rather than relying only on patient symptoms to inform targeting of cortical stimulation, a multimodal brain imaging approach is of interest.

II. Methods

A. MEG Recordings

The MEG procedure was approved by the IRB committee at the Medical College of Wisconsin. MEG data was acquired using the Elekta-Neuromag VectorView MEG system (306 sensors – 102 sensor triplets, each consisting of 2 orthogonal planar gradiometers and 1 planar magnetometer – that measure magnetic flux at 102 positions) at the MEG Program of Froedtert Hospital/The Medical College of Wisconsin. The subject was a tinnitus patient who provided fully-informed consent to participate to the study. He had been implanted with a cortical stimulation device (Northstar Neuroscience Inc.) in the left secondary cortical cortex. CS consisted of 40Hz pulse with a pulse width of 150 micro-seconds. The MEG sampling rate was set to 2KHz. The patient was instructed to stay still with eyes open while recorded spontaneous brain activity was recorded with CS being either turned on or off (2 separate 5 min recordings).

B. MEG Analysis

MEG data was first processed by the signal-space separation (SSS) [14] technique as available from Elekta's MaxFilter software. SSS applied a spatial filter to the MEG sensor data to reduce contamination from external sources (e.g., heart, muscles, and environmental nuisances such as the CS device). This procedure is further imposed by the active Maxshield (Elekta) shielding compensation solution in place at the recording site.

The data was then band-pass filtered (2-100Hz) to remove low-frequency drifts and high frequency noise and was further denoised using signal classification through signal-space projection (SSP). SSP projects the data time series away from the subspaces spanned by noisy components as identified in the data. Both filtering and SSP were performed using the freely available MNE software (MGH-Harvard Medical School). Spectral analysis of the processed data was completed using the multitaper Fourier transform to obtain the time-frequency spectral densities, log power spectrum, cross-spectral density matrices, and cross-frequency correlation indices at the MEG channel level. These MEG spectral markers have proved useful to characterize global oscillatory activity in multiple brain disorders, including tinnitus [7], [12], [13]. The processed data was then analyzed with Independent Component Analysis (ICA) [15]. ICA provides a decomposition of the original measurements into maximally independent time courses. ICA was implemented in Matlab using modified code obtained from the EEGLAB Toolbox. The time-frequency dynamics of the unfiltered independent source time-series were computed using multitaper spectral analysis as for sensor signals. Brain-related independent sources were sorted out from correlated noise sources both automatically by using a matched-filter approach, and manually by inspecting the spectrum of all independent sources.

Neuromagnetic source imaging was performed with a new robust matched filter algorithm with anatomical priors incorporated by only allowing activity to be constrained to the individual segmented cortical surface. MRI segmentation was performed from the subject's T1 scan using Freesurfer and MNE. The MEG forward model was obtained from the Boundary Element Method (BEM) with isolated-skull approach as implemented in MNE. Source estimates were computed for all independent components. The ICA mixing matrices were column normalized prior to localization and the activation functions were multiplied by their respective norms. Source estimates were visualized in inflated and folded cortical surfaces.

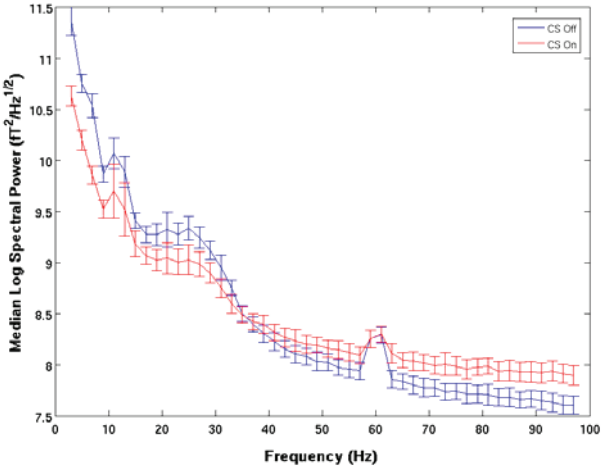

Fig 1. Sensor level spectral analysis. Multitaper power spectral density estimates were computed for denoised data and averaged across 3 tapers (5s time windows with 2.5s overlap). The log mean power was averaged across 2Hz frequency bins and across channels. A Wilcoxon rank sum test was run to test for differences between median log spectral power across time windows for CS off (blue) vs. CS on (red) conditions. Plot shows medians with error bars showing +/- standard deviations. Medians for all frequency bins were found being significantly different ($p<0.001$, with Bonferroni correction) except for bins within: [34-38], and [58-62] Hz.

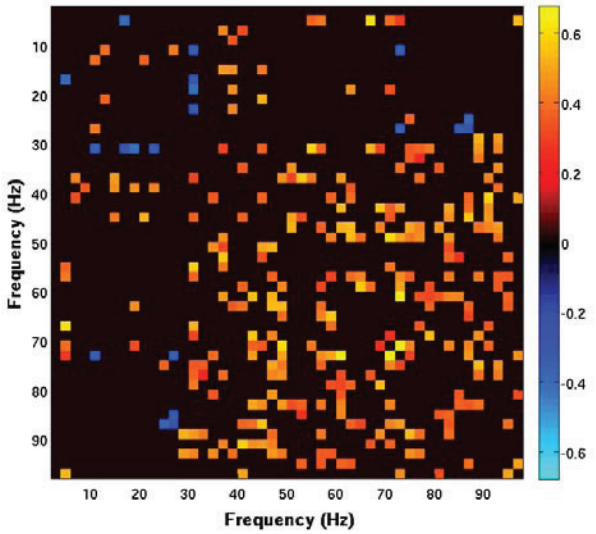

Fig 2. Sensor level power correlation analysis. The power correlation between frequency bands of the time-frequency log power (averaged across tapers and 2Hz frequency bins) was computed for CS on and CS off recordings. The contrast in power correlation (CS on – CS off) is shown here thresholded following a two-tailed permutation t-test with Bonferroni correction (p-value=$8.5*10^{-6}$). Positive correlation values (red-yellow) indicate a higher power correlation in the CS on condition, while negative correlation values (blue) indicate higher correlation in the CS off condition.

III. Results

A. Sensor level analysis

The spectrum of the processed MEG signals indicated that the measurements were highly contaminated by noise especially when the cortical stimulator was turned on. When the CS was turned off, even minor head movements produced strong noise artifacts due to the implanted CS device and associated wiring. When CS was turned on, CS produced subharmonic peaks in the spectrum because of aliasing due to the relatively limited sampling rate compared to the CS pulse width (150 micro-seconds). Nonetheless, careful application of SSP was able to remove both types of noise artifacts.

The spectrum of the denoised data showed the typical pink spectral distribution with a peak at alpha, and broad power in the beta and gamma ranges for both the CS on and off conditions (see Fig. 1). A Wilcoxon rank sum test showed that the power was significantly larger for the CS off condition than the CS on condition for the lower frequency bands ranging from 2 to 34Hz. In contrast, power was larger for the CS on condition compared to the CS off condition for the higher-frequency bands ranging between 38Hz and 100Hz, except within the 58-62Hz range (consistent 60Hz power line contamination across conditions).

The spectral power correlation analysis (see Fig. 2) revealed increased correlation of power across a wide gamma (30-100Hz) range while CS was on. Increased power correlation during CS was also found within the alpha band range with the beta, theta and CS frequency (40Hz), and between theta and high gamma. More power correlation was found when CS was off between alpha and low and high gamma (31 and 73Hz), and between theta and 17Hz, and between beta and low gamma, and between beta and high gamma.

B. Source level analysis

Since sensor signals are mixtures of sources, their time-frequency spectral content reflects the dynamics of the mixtures and not of the underlying sources. Thus, we also performed time-frequency analysis of the independent source activation functions obtained from ICA.

Neuromagnetic source imaging showed that multiple independent components localized to brain areas known to be spontaneously active during rest. These included mu rhythm sources localized to somato-motor cortices and alpha sources localized to striate and extrastriate visual cortices. We also found several tau rhythm independent components which localized to the left and right auditory cortices.

In Fig 3A, we show the power spectrum of a typical tau component obtained when CS was off, which in addition to exhibiting spontaneous oscillations in the alpha range, had several large peaks in the theta and delta bands as expected based on the TCD hypothesis. This source also had peaks and broad band power in the beta and gamma bands, as expected from a dysrhythmic source. The source estimate of this component localized to the left auditory cortices, which is in agreement with the subject's experience of tinnitus to the right side (Fig. 3B).

Fig 4A shows the spectra of four independent sources during CS, which localized to the left auditory cortices, insula, and nearby regions. The spectra show clear peaks in

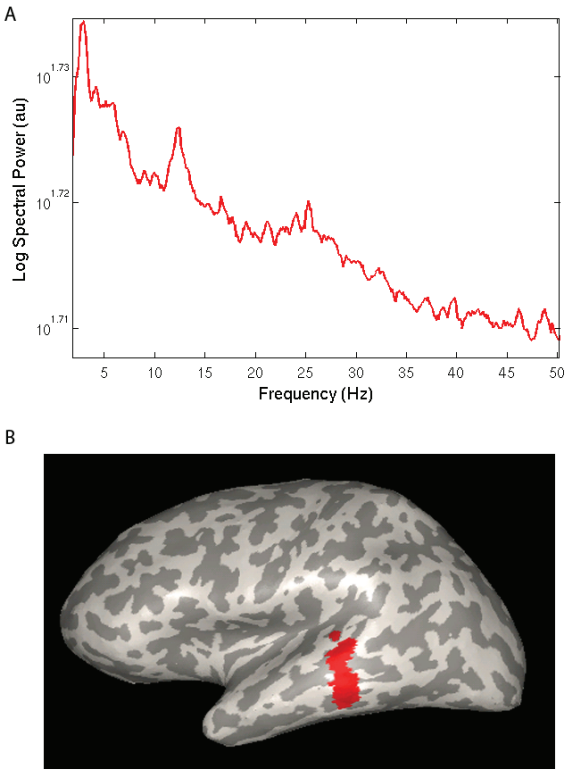

Fig 3. Independent theta/delta auditory source during no CS. (A) Spectrum averaged across tapers and time windows for independent component 10 with CS turned 'off'. (B) Source estimate of independent component using matched filter algorithm.

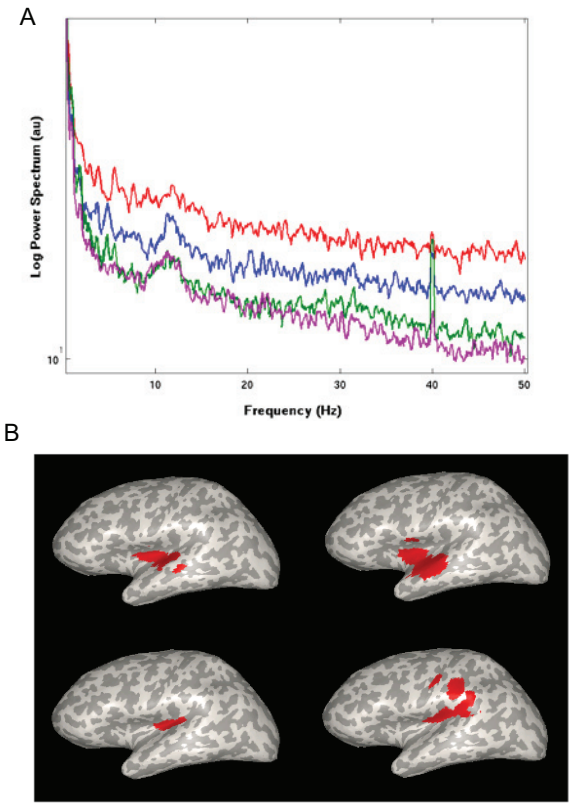

Fig 4. CS-modulated independent sources during CS. (A) Spectrum averaged across tapers and time windows for independent components 12, 36, 71, and 81 with CS turned 'on'. (B) Source estimate of independent components using matched filter algorithm.

the alpha band that were missing from the theta/delta source when CS was off. These sources exhibit smaller peaks in the theta band, but these latter are clearly reduced with respect to CS off. These sources also show power in the beta and gamma band, and also clearly show a peak at 40Hz, the stimulation frequency, which suggests that they might be entrained by CS.

Finally, Fig 5 shows the location of the cortical stimulation electrodes and the areas that were activated during an fMRI experiment using speech babble auditory stimuli.

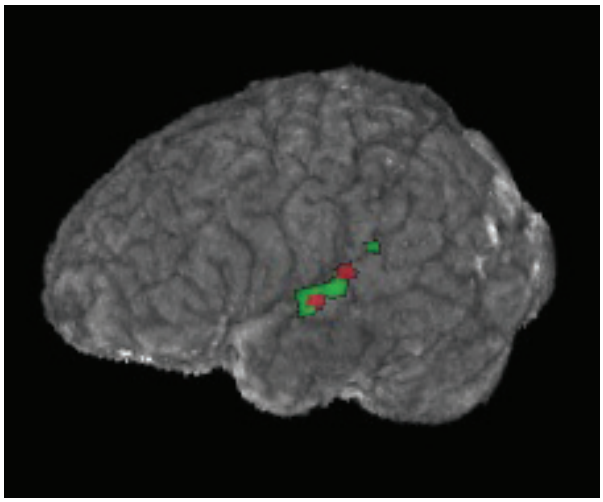

Fig 5. Location of cortical stimulation electrodes (in red) and fMRI signal in response to speech babble (in green).

IV. Discussion

These early results report on both global (sensor level) and regional (source level) effects of CS as revealed by MEG. Abnormal theta/delta activity was found in the left auditory cortices of the subjects when CS was off, consistent with his experience of tinnitus on the right side and consistent with the thalamocortical dysrhythmia hypothesis of tinnitus. When CS was turned on, several independent sources distributed in the left auditory cortices, insula, and surrounding regions were found. The activity of these sources showed spectral peaks in the alpha range suggesting that they were tau rhythm sources, and showed decreased theta/delta activity compared to the source identified during no CS. This result suggests that CS can suppress oscillations in the theta/delta bands while increasing tau oscillations. The sources identified in the CS condition had peaks at the CS frequency. The activity in the insular cortex may represent the affective component that usually accompanies tinnitus.

Thus, this suggests that CS may have a positive effect on affect by reducing the theta/delta activity in the insula. One of the sources extended to regions of the left somatosensory cortex. This may bear some significance since the patient reported that his tinnitus is sometimes modulated by somatosensory stimulation of the face. Importantly, the areas that were determined to exhibit abnormal theta/delta activity coincide with the location of the electrodes and the areas that were activated in the fMRI experiment. This coincides with the MEG source imaging results reported here and suggest that this patient responded well to CS because the stimulating electrodes were located in thalamocortically dysrhythmic regions of his brain.

V. Conclusion

This contribution proves the concept that simultaneous investigations of MEG brain responses to cortical stimulation in tinnitus is feasible and may reveal short-term modulation of brain ongoing activity both at the global and regional scales. Further investigations across a group of volunteers are certainly required but the methodology derived here opens wide, innovative perspectives towards a better understanding of CS on neuropsychological disorders and possibly, improved targeting and response to CS from a increasing number of patients.

References

[1] A. Davis and A. El Refaie, "Epidemiology of Tinnitus," in *Tinnitus Handbook.*, R. S. Tyler, Ed. San Diego: Singular Publishing Group, 2000.

[2] D. De Ridder, G. De Mulder, V. Walsh, N. Muggleton, S. Sunaert, and M. A., "Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus," *J. Neurosurg.*, vol. 100, pp. 560-564, 2004.

[3] D. De Ridder, G. De Mulder, E. Verstraeten, K. Van der Kelen, S. Sunaert, M. Smits, S. Kovacs, J. Verlooy, P. Van de Heyning, A. R. Moller, and "Primary and Secondary Auditory Cortex Stimulation for Intractable Tinnitus," *J. Otorhinolaryngol Relat Spec,*, vol. 68, pp. p. 48-54; discussion 54-5., 2006.

[4] A. J. Fenoy, M. A. Severson, I. O. Volkov, J. F. Brugge, and M. A. r. Howard, "Hearing suppression induced by electrical stimulation of human auditory cortex," *Brain Res*, vol. 1118, pp. 75-83, 2006.

[5] G. W. Friedland DR, Runge-Samuelson C, Ulmer JL, Kopell BH, "Feasibility of Auditory Cortical STimulation for the Treatment of Tinnitus," *Otol & Neurotol*, vol. 28, pp. 1005-12, 2007.

[6] H. Ashton, K. Reid, R. Marsh, I. Johnson, K. Alter, and T. Griffiths, "High Frequency Localised "Hot Spots" in Temporal Lobes of Patients with Intractable Tinnitus: A Quantitative Electroencephalographic (QEEG) Study," *Neurosci Lett*, vol. 426, pp. 23-8, 2007.

[7] R. Llinás, F. J. Urbano, E. Leznik, R. R. Ramírez, and H. J. van Marle, "Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect," *Trends in Neuroscience*, vol. 28, pp. 325-33, 2005.

[8] N. Weisz, S. Moratti, M. Meinzer, K. Dohrmann, and T. Elbert, "Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography," *PLoS Med.* , vol. 2, pp. e153, 2005.

[9] N. Kahlbrock and N. Weisz, "Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power," *BMC Biol.* , vol. 6, 2008

[10] K. Dohrmann, N. Weisz, W. Schlee, T. Hartmann, and T. Elbert, "Neurofeedback for treating tinnitus," *Prog Brain Res.* , vol. 166, pp. 473-85, 2007.

[11] W. Schlee, T. Hartmann, B. Langguth, and N. Weisz, "Abnormal resting-state cortical coupling in chronic tinnitus," *BMC Neuroscience 2009.*, vol. 10:11, 2009.

[12] S. J. Jeanmonod D, Ramirez R, Cancro R, Lanz M, Morel A, Magnin M, Siegemund M, Kronberg E, Ribary U, Llinas R., "Neuropsychiatric thalamocortical dysrhythmia: surgical implications.," *Neurosurg Clin N Am.* , vol. 14, pp. 251-65, 2003

[13] R. R. Llinás, U. Ribary, D. Jeanmonod, E. Kronberg, and P. P. Mitra, "Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by MEG," *PNAS USA.* , vol. 96, pp. 15222-7, 1999.

[14] S. Taulu, M. Kajola, and J. Simola, "Suppression of interference and artifacts by the Signal Space Separation Method," *Brain Topography.* , vol. 16, pp. 269-275, 2004.

[15] S. Makeig, T. P. Jung, A. J. Bell, D. Ghahremani, and T. J. Sejnowski, "Blind separation of auditory event-related brain responses into independent components," *PNAS U S A.* , vol. 94, pp. 10979-10984, 1997.